REMARKS

Status of the Claims

Claims 1, 3 and 5-11 are currently pending in this application. Claims 2, 4 and 12 were previously canceled. Claims 1, 3 and 5-11 were examined and rejected.

In this amendment, claim 11 has been canceled; claims 1, 3 and 5-10 have been amended; and new claims 13-25 have been added. Support for the amendment may be found throughout the application as filed, for example, at pages 6 through 8. Thus, no new matter has been added. Upon entry of the amendment, claims 1, 3, 5-10 and 13-25 will be subject to further examination. Entry of the amendment and reconsideration in view of the following comments is respectfully requested.

Rejection under 35 U.S.C. § 101

Claims 1, 3 and 5-11 are rejected under 35 U.S.C. § 101 because the claimed invention is allegedly directed to non-statutory subject matter, namely to processes for reconstructing the metabolism of a mammalian organism in disease and non-disease states and for identifying drug targets by comparing differences between metabolic maps of disease and non-disease states.

Without acquiescing to the Office's reasoning and solely to advance prosecution of this application, Applicants have amended independent claims 1 and 3 to recite articles of manufacture comprising a computer-readable medium having embodied thereon a set of program instructions configured to enable a computing device to perform methods for reconstructing mammalian metabolism (claim 1) and for identifying drug targets (claim 3). All the dependent claims have been amended accordingly. As noted above, written support for this amendment may be found in the original application at least at page 6, second and third paragraphs (e.g., "Structured annotation allows the organization of heterogeneous data and the development of queries and computer algorithms that can track explicit and implicit links among these data" and "In order to organize the information collected in the process of reconstruction, a relational database has been developed using Oracle RDBMS"). A person skilled in the art would easily recognize that this invention

clearly refers to computer-implemented methods and therefore requires a computer-readable medium embodying a set of program instructions configured to enable a computer to perform the recited method steps.

In a recent post-*Bilski* decision, the Board of Patent Appeals and Interferences confirmed this claim type (i.e., "Beauregard Claim") as patentable even in view of *In re Nujten*:

> It has been the practice for a number of years that a "Beauregard Claim" of this nature be considered statutory at the USPTO as a product claim. (MPEP 2105.01, I). Though not finally adjudicated, this practice is not inconsistent with *In re Nuijten*. Further, the instant claim presents a number of software components, such as the claimed logic processing module, configuration file processing module, data organization module, and data display organization module, that are embodied upon a computer readable medium. This combination has been found statutory under the teachings of *In re Lowry*, 32 F.3d 1579 (Fed. Cir. 1994). In view of the totality of these precedents, we decline to support the rejection under 35 U.S.C. § 101.
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> (*Ex parte Bo Li*, Appeal 2008-1213 (BPAI 2008) at page 9, emphasis added.)

Accordingly, it is respectfully submitted that the present claims as amended constitute patentable subject matter, and therefore this rejection under 35 U.S.C. § 101 may properly be withdrawn.

Rejections under 35 U.S.C. § 103

Nakao in View of Karp and Kuffner

Claims 1, 3, 5 and 7-10 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nakao *et al.* (*Genome Informatics* 1999, 10:94-103, hereinafter "Nakao") as supported by the KEGG table of contents as of February 1999 (hereinafter "KEGG", *available at*: http://web.archive.org/web/19990203053246/www.genome.ad.jp/kegg/kegg2.html), in view of Karp *et al.* (*Trends in Biotech.* 1999, 17:275-281, hereinafter "Karp") and Kuffner *et al.* (*Bioinformatics*, 2000, 16(9): 825-836, hereinafter "Kuffner").

The Office asserts that Nakao discloses a method of metabolism reconstruction for both normal and disease states, wherein data regarding a eukaryotic organism's metabolism is collected, the data are linked to metabolic pathways, and interconnections are identified to create a map of the organism's metabolism. The Office acknowledges that Nakao does not teach identification of drug targets. To cure this deficiency of Nakao, the Office cites Karp, which allegedly teaches that new drug targets may be identified through the analysis of pathway genome databases and that that integrated genome-metabolic pathways provide a framework for improved drug discovery. The Office further cites Kuffner, which allegedly teaches a method for combining the information found in various metabolic databases to produce a differential metabolic display (DMD), which allows the comparison between disease pathways and non-disease pathways. The Office asserts that it would have been obvious to one of skill in the art to modify the method of reconstructing an organism's metabolism of Nakao with the drug target identification of Karp because Karp teaches that that integrated genome-metabolic pathways provide a framework for improved drug discovery. The Office further asserts that it would have been obvious to modify the method of reconstructing metabolism with collected data of Nakao and the use of pathways to identify targets of Karp with the DMDs of Kuffner because Kuffner teaches that DMDs allow the display of significant differences in order to identify gaps in specific pathways and enable the interpretation of expression data by making predictions for proteins of unknown function and to propose the existence and/or absence of specific proteins or protein functions. Applicants respectfully traverse this rejection for the reasons of record and for the additional reasons set forth below.

The obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter must be considered. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)). To establish a *prima facie* case of obviousness a three-prong test must be met. First, the prior art reference must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). Second, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference to achieve the claimed invention.

KSR at 1731. And third, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

As an initial matter, independent claims 1 and 3 have been amended as set forth above, and a new independent claim 19 has been added, which is directed to prediction of novel enzymes. As noted above, support for the amendment and for the new claim may be found in the original application at least on pages 6 through 8. All of the remaining claims depend directly or indirectly on claims 1, 3 and 19, thereby incorporating their limitations.

As Applicants have pointed out in the remarks accompanying the Preliminary Amendment filed on January 21, 2009, one of the key differences between the claimed invention and the teachings of Nakao is that the present invention reconstructs mammalian metabolism "from scratch" (i.e., solely on the basis of mammalian experimental data), whereas Nakao merely superimposes mammalian genomic data on generalized metabolic pathways that are generated from all kinds of eukaryotic and prokaryotic systems. Thus, even though Nakao discloses organism-specific metabolism reconstruction, this reconstruction is accomplished using a conceptually different approach that necessarily yields different results. The Office quotes the following passages:

> It is now possible to make use of expression data for the reconstruction of pathways from the complete genome sequences. (Nakao, Abstract).
>
> To effectively analyze the new type of data derived from the expression profiles we should integrate them with the functional data such as pathways and assemblies, as well as with the traditional molecular biology data such as nucleotide and amino acid sequences. (Nakao at page 94, paragraph 1, lines 3-5).
>
> One of the main features of KEGG is a collection of pathway maps, which computerizes the network information of molecular interactions such as for metabolism and signal transduction. Another feature of KEGG is a collection of genome maps for completely sequenced organisms, as well as for the fruit fly, mouse, and human. (Nakao at page 94, paragraph 2, lines 6-9).
>
> In this paper, we report an integration of gene expression data into the DBGET/LinkDB and KEGG systems and show how we can make use of the integrated system for analysis of expression data. The integration includes a visualization of genome-scale gene expression data not only by the standard array view but also by the genome map and pathway map views. The analysis includes a metabolic pathway reconstruction by differential gene expression patterns

> obtained by comparison of the reference state and the perturbed state (e.g. the wild-type and a disruptant, or the control and an environmental shift). (Nakao at page 94, paragraph 3, lines 1-3; page 95, lines 1-4).

The cited passages are consistent with the Applicants' stated position that Nakao teaches a conceptually different method of metabolism reconstruction wherein generalized metabolic maps are prepared manually, after which organism-specific genomic data are automatically combined with these generalized pathways to match specific genes with enzyme placeholders on the generalized maps. The distinction is made clear in a number of other papers describing KEGG:

> One of the most unique aspects of KEGG is the automatic generation of organism-specific pathways by matching the gene catalogs being produced by the genome sequencing projects and the reference pathway diagrams manually drawn and updated. (M. Kanehisa, "A database for post-genome analysis," *Trends Genet.* 13:375-376 (1997), attached as ***Exhibit A***, at page 376, left column).
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> Because the metabolic pathway, especially for intermediary metabolism, is well conserved among most organisms from mammals to bacteria, it is possible to manually draw one reference pathway and then to computationally generate many organism-specific pathways. (M. Kanehisa & S. Goto, "KEGG: Kyoto Encyclopedia of Genes and Genomes," *Nucleic Acids Res.* 28(1):27-30 (2000), attached as ***Exhibit B***, at page 29, left column; emphasis added).
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> For each pathways diagram there is one reference diagram which is manually drawn and updated, and all organism specific diagrams are computationally derived by matching the enzyme objects and the corresponding genes in the gene catalogue… In order for this procedure to be successful, the reference diagram should contain all known alternatives of reaction paths rather than just the consensus alone. (H. Ogata *et al.*, "Computation with the KEGG pathway database," *BioSystems* 47:119-128 (1998), attached as ***Exhibit C***, at page 121, left column to page 122, right column; emphasis added).
>
> The KEGG reference maps for metabolic pathways represent biochemical knowledge containing all chemically identified reaction pathways. The constraint on the genome, i.e., a list of enzymes encoded in the genome, will reconstruct organism-specific pathways, which are represented by coloring of boxes in the KEGG pathways maps (Fig. 1). (H. Ogata *et al.*, "KEGG: Kyoto Encyclopedia of Genes and Genomes," *Nucleic Acids Res.* 27(1):29-34 (1999), attached as ***Exhibit D***, at page 33, right column; emphasis added).

Thus, the KEGG approach to metabolic reconstruction relies on a generic, multi-species conceptualization of pathways. A KEGG pathway is defined as the sum total of all reactions related

to that pathway that have been observed across a number of organisms. Notably, that generic pathway may not occur in its entirety in any one organism. When performing a pathway prediction for a new organism, the KEGG group merely superimposes on the generic pathway diagram those enzymes present in the genome of that organism. They do not build distinct database objects for the different variants of a pathway that exist in different species and so cannot encode the pathway exactly as it is postulated to occur in that species, nor do they take into account experimental information about what pathway variant is present in a given species. For all these reasons, the KEGG approach to pathway reconstruction frequently results in errors and inconsistencies stemming from divergent metabolic pathways in different species. In contrast, the present invention uses experimental information from a mammalian (e.g., human) organism to reconstruct organism-specific pathways from the ground up. Advantages of this approach are stated as follows:

> This allows the imposition of a condition of self-consistency on the resulting networks. This means that each metabolite should either be essential for the organism (e.g., consumed through food) or there should be a pathway that produces it. In other words, if there is a gap between two nonessential compounds, this implies a lack of knowledge and serves to direct further research.
>
> This allows the prediction of the existence of an enzyme function in an organism even if organism-specific genes or proteins have not been identified. For example, when there is a clear gap between two metabolites in the reconstruction that cannot be filled in by any of the described enzymes, it is predicted that there is at least one undescribed enzyme that bridges this gap. In the present reconstruction of amino acid metabolism in humans, several human enzymes were identified that had not been previously identified in the human genome. These enzymes were identified because their functions were required by the logic of the metabolic map. Consequently, human genes for these enzymes were proposed through thorough similarity searches of the human genome and by studying human ESTs.
>
> The self-consistency condition also helps eliminate pathways that might be incorrectly assigned merely on the basis of human enzymes having been identified. One example can be illustrated with phenylalanine biosynthesis. It is well known that humans cannot synthesize this essential amino-acid. However, there is a human enzyme, aspartate transaminase (EC 2.6.1.1), that could potentially synthesize phenylalanine from phenylpyruvate. Simply superimposing the human enzyme onto a general metabolic map would lead to the incorrect conclusion that there is a human pathway for phenylalanine biosynthesis. In contrast, the self-consistent reconstruction of the present invention shows that the

> absence of phenylpyruvate, the substrate for aspartate transaminase, makes biosynthesis of phenylalanine improbable in humans.
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> (The specification at pages 8-9; emphasis added).

In order to emphasize the distinction between the present invention and the teachings of Nakao, step (e) of claims 1 and 3 has been amended to recite "creating and displaying interactive maps of the mammalian organism's metabolism in said non-disease and disease states exclusively on the basis of information obtained in steps (a) through (d)," i.e., without using a generic "reference" metabolic pathway generated using information from other species.

As noted in the preliminary Amendment filed on January 21, 2009, neither Karp nor Kuffner contains a single reference to mammalian metabolic pathways. Both of these cited references are focused on metabolic reconstruction of microbial organisms. Consequently, even if a skilled artisan somehow managed to integrate the PATHWAY system of Nakao with the PathoLogic system of Karp and/or the DMD system of Kuffner – which would represent a major technological feat given that these systems are based on distinct modeling algorithms – the resulting combination would still fall short of disclosing each and every element of the claimed invention. As noted previously, both the software tools and the scientific information available at the time the cited prior art documents were published were inadequate to practice the claimed invention. Accordingly, Applicants respectfully submit that the Office has failed to establish *prima facie* obviousness, and therefore this rejection under 35 U.S.C. § 103(a) should be withdrawn.

Nakao in View of Karp and Kuffner and Further in View of Okubo

Claim 6 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nakao as supported by KEGG, in view of Karp and Kuffner as applied to claims 1, 3 and 5 above, and further in view of Okubo *et al.* (*Nature Genetics* 1992, 2:173-179, hereinafter "Okubo").

The Office acknowledges that Nakao in view of Karp and Kuffner as applied to claims 1, and 5 above does not teach the use of EST data, as recited in the instant claim 6. To cure this deficiency of Nakao, Karp and Kuffner, the Office cites Okubo, which allegedly teaches the use of EST data for gene mapping. The Office asserts that it would have been obvious to one of skill in

the art to modify the method of metabolism reconstruction of Nakao in view of Karp and Kuffner as applied to claims 1 and 3-5 by incorporating the EST data of Okubo because Okubo teaches that a map of expressed genes will facilitate the search for biologically and industrially interesting genes.

Since Okubo is cited specifically for its teaching of the EST limitation, this reference does not cure the deficiencies of Nakao in view of Karp and Kuffner as applied to claims 1, 3 and 5 above. Accordingly, Applicants respectfully submit that this rejection should also be withdrawn.

Nakao in View of Karp and Kuffner and Further in View of Kumar and Tile D4

Claim 11 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nakao as supported by KEGG, in view of Karp and Kuffner as applied to claims 1, 3 and 5 above, and further in view of Kumar (*React. Funct. Polymers*, 2000, 46: 1-27, hereinafter "Kumar") and Tile D4 of the Boehringer Biochemical Pathways Map (Roche Applied Science, 1993, *available at*: http://www.expasy.org/cgi-bin/show_image?D4&up, hereinafter "Tile D4").

This rejection is rendered moot by the cancellation of claim 11.

Non-Statutory Double Patenting

Claims 3, 7 and 8 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1 and 4 of copending Application No. 11/499,437. The Office asserts that although the conflicting claims are not identical, they are not patentably distinct from each other.

Since this is a provisional obviousness-type double patenting rejection over a later filed co-pending application, it is respectfully requested that the rejection be held in abeyance until patentable subject matter is found, and that the rejection be withdrawn if it is the only remaining rejection (*see* MPEP § 804.I.B: "If a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer").

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 655202000300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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